

# NIEHS News

## Getting a Grip on Slippery DNA

Each human cell contains the complete plan and operating instructions for the entire body, in a library composed of 6 billion nucleotides. This information, roughly the equivalent of 1000 volumes of a large college textbook, can be copied in about 8 hours. Amazingly, this process occurs almost perfectly; the error rate inside a human cell may be less than one mistake per genome.

The near-perfection of this process makes the rare errors especially fascinating and significant to scientists. Thomas A. Kunkel, in the NIEHS Laboratory of Molecular Genetics, leads a multidisciplinary team of researchers from various NIEHS labs in pursuit of the secrets of these errors, which researchers have related to genetic diseases including fragile X syndrome, myotonic dystrophy, Kennedy's disease, Huntington's disease, spinocerebellar ataxia type 1, and cancers including colon, gastric, pancreatic, and endometrial. Kunkel notes that these mistakes in the replication process provide useful biological markers in people susceptible to these diseases. The studies also offer insights to the mechanisms through which these genetic diseases and cancers occur and perhaps how they might relate to environmental exposures.

The term "slippery DNA" describes the slippage of one strand of DNA relative to another, the copied strand relative to the template strand. This repositioning causes basepairs to be skipped or added during replication, thus scrambling the genetic information to produce an incoherent message. To help those outside the field better understand the principles at work, Kunkel uses the metaphor of typing. He notes that a typist has the opportunity to correct errors as he or she goes along; likewise, incorrectly copied nucleotides may be corrected as replication is in progress. Later, in the same way that a proofreader catches errors in text and replaces whole words or sentences, the cell "proofreads" its work and can remove incorrectly copied sequences of nucleotides and replace them with corrected ones. Kunkel notes that for a typist to duplicate the feat routinely performed by the cell, he or she would have to type all of the contents of a fairly large personal library with one or zero errors in eight hours.

Despite the cell's incredible capability, when errors are not caught and corrected, they give rise to genetic diseases and cancers, although the mechanisms by which these diseases arise have yet to be defined. Further, some genetic errors seem to be amplified in the next generation, as with the retardation associated with the fragile X syndrome, that becomes more severe in successive generations.

Kunkel described the current state of research on slippery DNA as "a ripe opportunity for rapid understanding of biological phenomenon." His review article on the subject appeared in the September 16 issue of *Nature*.

## Two New Environmental Health Sciences Centers Funded

The first two Environmental Health Sciences Centers to be established since the development of new center guidelines by NIEHS in 1992 were funded April 1 at Wayne State University in Detroit and the University of Arizona at Tucson. The two new centers bring the number of NIEHS Environmental Health Sciences Centers to 15; the NIEHS centers program also includes five Marine and Freshwater Biomedical Sciences Centers and a Developmental Center, with at least one additional Developmental Center planned. When the two new centers were funded, another three existing centers had their grants renewed: Vanderbilt University, University of California, Berkeley and Massachusetts Institute of Technology.

The center at Wayne State, under the direction of Raymond F. Novak, will focus on molecular and cellular toxicology with human applications. The center will feature research cores on regulation of gene expression, signal transduction, epidemiology, and biostatistics. To support these programs the center maintains facilities for transgenic animals, cell image analysis, immunocytochemistry, *in situ* hybridization, and cell culture.

The center at the University of Arizona at Tucson has formed four interdisciplinary programs: biotransformation, metals, cell injury, and environmental genetics. Center Director Glenn I. Sipes, said that the programs will be supported by five service cores: synthetic chemistry, analytical services, experimental pathology, *in*

*vitro* systems, and biomathematics/molecular modeling. A transgenic animal facility will also be developed to serve the programs.

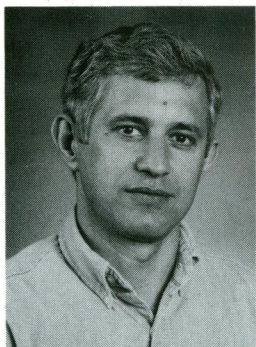
"The Environmental Health Sciences centers are a national resource for multidisciplinary approaches to problems in human environmental health, and as a group they form a network that fosters communication, innovation, and high-quality research," said Kenneth Olden, NIEHS director. The centers provide a stimulating, multidisciplinary working environment that attracts both established and promising young investigators, according to Olden. They are also a key source of expertise on emerging issues in environmental health and a means for communicating environmental health issues to the public and to elected officials. New NIEHS center guidelines include requirements for community outreach and education programs, which foster involvement with local and regional environmental health issues.

Applications for centers are submitted through the Division of Research Grants at the National Institutes of Health in Bethesda, Maryland, and then assigned to the appropriate institute. Applications received assigned to NIEHS are reviewed on a competitive basis and, if appropriate, approved by the National Environmental Health Sciences Advisory Council, one of the institute's principal governing bodies.

## Capturing the Spirit of Science Education

Who will be the environmental health scientists of the future? What makes students develop an interest in science so that they ultimately choose a research career? NIEHS is taking an active role in answering these questions through a variety of education outreach efforts designed to introduce students to the field of environmental science. The outreach program relates experiences that encourage students to consider science careers, and it helps students gain general knowledge about environmental science at the same time.

Years ago, former NIEHS Director David P. Rall noted that along with its basic biomedical research mission, NIEHS is also an educational institution. In those days, the emphasis was on graduate students and postdoctoral scientists and in fact guidelines for NIEHS Environmental Health Sciences Centers grants include education and community outreach requirements at each of the 15 centers nationwide. In recent years, under the



**Repair man.** Thomas A. Kunkel leads a team studying DNA replication errors.